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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
BERTOGLIO, VALERIE E

ART UNIT	PAPER NUMBER
1632	

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8

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/005,169	Applicant(s) GUENTHER ET AL.	
	Examiner Valarie Bertoglio	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *1-4,11-13,16,17 and 20-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-10, 14,15,18 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action* .

Election/Restrictions

Applicant's election with traverse of Invention III, claims 8,10,14,15,18 and 19 in paper No. 5 is acknowledged. Applicant's arguments are found partially persuasive and Inventions II and III will be rejoined and Inventions VII and VIII will be rejoined.

The traversal is partially on the ground(s) that a search of Invention I claims and Invention II-V or Invention VI claims together would not be an undue burden because a reasonable search would produce results related to the targeting construct of Invention I and the cells of Invention II or the animals of Invention III or the methods of screening using the transgenic animal of Invention IV, or using the transgenic cells of Invention V, or using the wild-type cells of Invention VI. This argument is not found persuasive because it is maintained that each of the inventions of Invention I and Invention II-V or VI require a separate search status on the basis of each of Inventions II-VI requiring a materially different product from that of Invention I, which is separately classified. In particular, Invention I is directed to methods of making a gene targeting construct that is not necessary to disrupt NOR1 in cells or in animals. Materially different constructs can be used to disrupt NOR1. Furthermore, the nucleic acid sequences of Invention I and the cells of Invention II or the animals of Invention III are structurally and functionally different. As such, Invention I and Invention II or Invention III require materially different reagents and technical considerations such that a proper search for both inventions would require an extensive search for materially different methods thereby placing an undue search burden upon the Examiner. Therefore, it is maintained that the Invention I

and Invention II-V or VI are distinct due to distinct structures, classification and method steps and are thus, separately classified and searched.

The traversal is partially on the ground(s) that a search of Invention I, II, or III claims and Invention VII claims together would not be an undue burden because a reasonable search would produce results related to the targeting construct of Invention I, the cells of Invention II or the animal if Invention III and the method of treating impaired balance or motor coordination of Invention VII. This argument is not found persuasive because it is maintained that Invention I,II, or III and Invention VII require a separate search status on the basis of each method requiring a materially different product a (nucleic acid, a cell, or an animal and a compound that treats disease, wherein the compound is not the nucleic acid). A search of the construct would not produce art encompassing a method of ameliorating impaired balance or impaired motor coordination. Furthermore, examiner maintains the argument that Inventions I, II or III and Invention VII have distinct uses. For instance, the nucleic acid can be used as a probe, the cells or the animals can be used to test for the effects of NOR1 disruption on gene expression and the methods of Invention VII can be used to treat disease. Therefore, it is maintained that Invention I, II or III and Invention VII are distinct due to distinct structures and are thus, separately classified and searched.

The traversal is partially on the ground(s) that a search of Invention I –VI or VII and Invention VIII claims together would not be an undue burden because a reasonable search would produce results related to each invention. This argument is found persuasive to the extent that a search of the claims of Invention VII would produce

results for the claims of Invention VIII. However, the argument not found persuasive as it relates to Inventions I-V or VI and Invention VIII because it is maintained that each of Invention I, Inventions II-IV, Invention V, or Invention VI require a separate search status. A search of the construct, the transgenic cells or animals, or the methods of screening for NOR1 modulators would not produce art encompassing a method of ameliorating impaired balance or impaired motor coordination using NOR1. Furthermore, Invention I, Inventions II-IV, Invention V, or Invention VI each are classified separately from Inventions VII and VIII. Therefore, it is maintained that the Invention I –V or VI and Inventions VII and VIII are distinct due to distinct structures and are thus, separately classified and searched.

The traversal is partially on the ground(s) that a search of Invention II claims and Invention IV claims together would not be an undue burden because a reasonable search would produce results related to the cells of Invention II and the method of screening compounds using a non-human transgenic animal. This argument is not found persuasive because a search of the cells with a disruption of NOR1 (Invention II) would not produce art encompassing a method of screening for modulators using a transgenic animal. Furthermore, the cells of Invention II have a separate patentable use from the methods of Invention IV as they can be used to determine the cellular effects of disrupting NOR1 expression. Therefore, it is maintained that Invention II and Invention IV are distinct due to distinct methods and structures and are thus, separately classified and searched.

The traversal is partially on the ground(s) that a search of Invention II claims and Invention V or VI claims together would not be an undue burden because a reasonable search would produce results related to the cells of Invention II and the method of screening using cells with a disruption in NOR1 (Invention V) or cells expressing NOR1 (Invention VI). This argument is not found persuasive because a search of the cells with a disruption of NOR1 (Invention II) would not produce art encompassing a method of screening for modulators using cells expressing NOR1 Invention VI). Furthermore, the cells of Invention II have a separate patentable use from the methods of Invention V as they can be used to make transgenic animals. Therefore, it is maintained that Invention II and Invention V or VI are distinct due to distinct methods and structures and are thus, separately classified and searched.

The traversal is partially on the ground(s) that a search of Invention II or III claims and Invention VII claims together would not be an undue burden because a reasonable search would produce results related to the knockout cells of Invention II or the knockout animals of Invention III and the method of treating impaired balance or motor coordination of Invention VII. This argument is not found persuasive because it is maintained that each of the inventions of Invention II or III and Invention VII requires a separate search status on the basis of each method requiring a materially different product a (cells or an animal and a compound that treats disease). Furthermore, examiner maintains the argument that Inventions II or III and Invention VII have distinct uses. For instance, the cells or the animals can be used to test for the effects of NOR1 disruption on gene expression and the methods of Invention VII can be used to treat

disease. Therefore, it is maintained that Invention II or III and Invention VII are distinct due to distinct structures and are thus, separately classified and searched.

The traversal is partially on the ground(s) that a search of Invention III claims and Invention IV claims together would not be an undue burden because a reasonable search would produce results related to the non-human transgenic animal of Invention III and the method of screening compounds using a non-human transgenic animal. This argument is not found persuasive because a search of the transgenic animal with a disruption of NOR1 (Invention III) would not produce art encompassing a method of screening for modulators of NOR1 expression or function. The transgenic animal is not necessary to screen for modulators of NOR1. Furthermore, the inventions are patentably distinct because the transgenic animals have a distinct use in that they can be used to determine the role of NOR1 in vivo. Therefore, it is maintained that Invention III and Invention IV are distinct due to distinct methods and structures and uses and are thus, separately classified and searched.

The traversal is partially on the ground(s) that a search of Invention III claims and Invention V or VI claims together would not be an undue burden because a reasonable search would produce results related to the transgenic knockout animals of Invention III and the method of screening using cells with a disruption in NOR1 (Invention V) or cells expressing NOR1 (Invention VI). This argument is not found persuasive because a search of the animals with a disruption of NOR1 (Invention III) would not produce art encompassing a method of screening for modulators using cells with a disruption in NOR1 (Invention V) or using cells expressing NOR1 (Invention VI). Furthermore, animal

is classified separately from the cells and is structurally and functionally distinct from the cells. Therefore, it is maintained that Invention III and Invention V or VI are distinct due to distinct methods and structures and are thus, separately classified and searched.

The traversal is partially on the ground(s) that a search of Invention IV claims and Invention V or VI claims together would not be an undue burden because a reasonable search would produce results related to methods of using the transgenic knockout animals of Invention IV and the method of screening using cells with a disruption in NOR1 (Invention V) or cells expressing NOR1 (Invention VI). This argument is not found persuasive because a search of methods of using the animals with a disruption of NOR1 (Invention IV) would not produce art encompassing a method of screening for modulators using cells with a disruption in NOR1 (Invention V) or using cells expressing NOR1 (Invention VI). Furthermore, animal is classified separately from the cells and is structurally and functionally distinct from the cells and the methods of using transgenic animals have different technical considerations than methods of using cells. Therefore, it is maintained that Invention III and Invention V or VI are distinct due to distinct methods and structures and are thus, separately classified and searched.

The traversal is partially on the ground(s) that a search of Invention IV, V or VI claims and Invention VII claims together would not be an undue burden because a reasonable search would produce results related to the methods of using transgenic knockout animals of Invention IV or the method of screening using cells with a disruption in NOR1 (Invention V) or using cells expressing NOR1 (Invention VI) and to methods of treating impaired balance or motor coordination. This argument is not found

persuasive because a search of methods of screening compounds would not produce art that encompasses methods of treatment. Furthermore, the purpose of Inventions IV-VI is different from Invention VII are classified separately from Invention VII. Therefore, it is maintained that Invention IV, V or VI and Invention VII are distinct due to distinct methods and structures and are thus, separately classified and searched.

The traversal is partially on the ground(s) that a search of Invention V and VI claims together would not be an undue burden because a reasonable search would produce results related to the methods of both inventions. This argument is not found persuasive because a search of methods of screening compounds that inhibit NOR1 would not necessarily encompass compounds that modulate NOR1. Furthermore, the cells of Inventions V and VI are genetically, structurally, and functionally distinct and have separate, patentable uses. Therefore, it is maintained that Invention V and VI are distinct due to distinct methods and structures and are thus, separately classified and searched.

With exception of arguments directly pertaining to Inventions II and III, which are rejoined or to Inventions VII and VIII which have been rejoined, the restriction requirement is still deemed proper and is therefore made **FINAL.**

Claims 1-26 are pending, however, claims 1-4, 11-13, 16,17 and 20-26 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions, the requirement having been traversed in Paper No. 5. Claims 5-10,14,15,18 and 19 are under current examination.

Specification

The disclosure is objected to because of the following informalities:

In the Brief Description of the Drawings, page 8, line 4 should begin "3B" not "2B".

Page 47, line 10 refers to Figure 2. The targeting construct is depicted in Figure 3, not in Figure 2.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-9,14,15,18, and 19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 5-9,14,15,18, and 19 encompass more than one NOR1 gene as they are drawn to "a NOR1 gene". The claims encompass any NOR1 gene that may exist in each and every species of animal. The specification teaches only one mouse NOR1 gene (SEQ ID NO: 1; page 7, line 30) and does not disclose that other NOR1 genes

exist or have the same function as the NOR1 gene disclosed. Therefore, adequate written description to support the claims encompassing more than the one, disclosed NOR1 gene is lacking.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieve regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the NOR1 gene encompassed by SEQ ID NO: 1, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 8-10, 14, 15, 18 and 19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a mouse or mouse cell whose genome comprises a homozygous disruption in the mouse NOR1 gene wherein said mouse exhibits increased or enhanced pain threshold or impaired balance and impaired motor coordination, does not reasonably provide enablement for any transgenic non-

human animal or cell of any species with a disruption of any NOR1 gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 8,14,15 and 16 are directed to a non-human transgenic animal with a disruption in the NOR-1 gene, wherein the transgenic animal exhibits increased or enhanced pain threshold (claim 14) or impaired balance and impaired motor coordination (claim 16). Claims 10, 18, and 19 are directed to a transgenic mouse with a disruption in the NOR1 gene, wherein said mouse exhibits increased or enhanced pain threshold (claim 18) or impaired balance and impaired motor coordination (claim 19).

The state of the art at the time of filing was such that one of skill could not predict the phenotype of transgenics. Leonard (1995, Immunological Reviews, Vol. 148, pages 98-113) disclosed mice with a disruption in the g_c gene which were intended to be a model for X-linked severe combined immunodeficiency (XSCID), but display a variety of unexpected traits (abstract). These knockout mice were expected to have thymocytes with decreased proliferation in response to stimulation with antibodies, but the thymocytes proliferated normally (page 105, line 7). Moens (1993, Development, Vol. 119, pages 485-499) taught two mutations produced by homologous recombination in two different locations of the N-myc gene produce two different phenotypes in mouse embryonic stem cells, one leaky and one null (page 486, column 1, first full paragraph). Griffiths (1998, Microscopy Research and Technique, Vol. 41, pages 344-358) teaches that, despite a known role for the PLP gene based on spontaneous mutations in the

gene, the knockout mouse failed to display any of the expected phenotypes (page 350, last paragraph). Thus, the phenotype of knockout mice was unpredictable.

The species-specific requirements for transgene design are not clearly understood. Examples in the literature aptly demonstrate that even closely related species carrying the same transgene construct can exhibit widely varying phenotypes. For example, several animal models of human diseases have relied on transgenic rats when the development of mouse models was not feasible. Mullins (1990, Nature, Vol. 344, 541-544) produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse *Ren-2* renin transgene. Hammer (1990, Cell, Vol. 63, 1099-1112) describe spontaneous inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human β_2-microglobulin transgenes. Both investigations were preceded by the failure to develop human disease-like symptoms in transgenic mice (Mullins, 1989, EMBO J., vol. 8, pages 4065-4072; Taurog, 1988, Jour. Immunol., Vol. 141, pages 4020-4023) expressing the same transgenes that successfully caused the desired symptoms in transgenic rats. Thus, the combination of elements (protein, promoter, species of protein, and species of transgenic) required to obtain a desired effect were not within the realm of routine experimentation at the time of filing.

Not only is the difference in transgenic mice and rats unpredictable for reasons stated above, the art at the time of filing was such that a number of significant limitations regarding the production of non-human transgenic animals existed. Wall (1996, Theriogenology, Vol. 45, pages 57-68) disclosed the unpredictability of transgene

behavior due to factors such as position effect and unidentified control elements resulting in a lack of transgene expression or variable expression (paragraph bridging pages 61-62). Overbeek (1994, "Factors affecting transgenic animal production," Transgenic animal technology, pages 96-98) taught that within one litter of transgenic mice, considerable variation in the level of transgene expression occurs between founder animals and causes different phenotypes (page 96, last paragraph). Therefore, it was unpredictable at the time of filing what gene of interest, promoter, enhancer, coding, or non-coding sequences present in the transgene construct, site of integration, method used and phenotype obtained were required to make a transgenic non-human mammal of interest.

The art at the time of filing further held that targeted gene insertion technology was not available for any species other than mouse. Since homologous recombination is required for gene targeting methods, embryonic stem cell technology must be available to carry out the method. Mullins (1996, J. Clin. Invest., Vol. 98, pages S37-S40) teach that non-mouse ES cells capable of providing germline chimeras were not available (page S38, column 1, first paragraph). Campbell and Wilmut (1997, Theriogenology, vol. 47, pp, 63-72) acknowledge reports of ES-like cells in a number of species, but emphasize that as yet there are no reports of any cells lines that contribute to the germ line in any species other than mouse (page 65). Furthermore, other potential methods of generating transgenic embryos using homologous recombination had not been developed at the time the invention was made (McGreath, 2000, Nature, Vol. 405, pages 1066-1069; Kent-First, 2000, Nature Biotechnology, Vol. 18, pages

928-929; Dinnyes, 2002, Cloning and Stem Cells, Vol. 4, pages 81-90). Thus, at the time of filing, knockout animals could not be prepared for any species other than mouse.

1) The specification does not provide adequate guidance for one of skill in the art to generate non-human transgenic animals (claims 8,14, and 15) having a disruption in the NOR-1 gene in any species other than mouse. The methods of gene targeting such as employed in the instant invention require embryonic stem cells. The guidance offered in the specification is limited to the production of knockout mice using mouse ES cells and no teachings or guidance are offered in regard to how one would have prepared any other species of animal using targeted mutagenesis. The specification discloses that it was known in the art how to make transgenic animals in species other than mouse without the need for ES cells (page 10, lines 26-31 through page 11, lines 1-2). However, the art cited describes random transgene insertion rather than the targeted gene insertion of the claimed subject matter. Furthermore, the specification and the art at the time of filing fail to disclose any ES cells other than mouse ES cells that contribute to the germline. Without such guidance, it would require undue experimentation for one of skill in the art at the time of filing to make any transgenic, non-human animal with a disruption in the NOR1 gene.

2) Applicants fail to enable the making and/or using a transgenic having a phenotype other than increased or enhanced pain threshold or impaired balance and impaired motor coordination. The specification does not provide an enabled use for the knockout claimed that has a wild type phenotype, which is encompassed by claims 8,10,14, and 15. As set forth in the art, the phenotype of the transgenic was

unpredictable at the time of filing. The specification does not overcome the unpredictability inherent in generating knockout mice such that any phenotype could be obtained other than increased or enhanced pain threshold or impaired balance and impaired motor coordination. Without such guidance, it would require one of skill in the art at the time the invention was made, undue experimentation to determine how to obtain an phenotype other than increased pain threshold or decreased motor coordination.

3) The specification teaches that only mice homozygous for a disruption in NOR1 displayed increased pain threshold or decreased motor coordination (page 48, line 11; page 48, line 24). The specification did not disclose a phenotype for mice heterozygous for a NOR1 disruption. Therefore, the claims should be limited to a homozygous disruption of the NOR1 gene.

4) The specification fails to enable disrupting any NOR1 gene in a mouse or another species or a cell other than a mouse cell. The specification only teaches one, mouse NOR1 gene (SEQ ID NO: 1; page 7, line 30). The specification does not provide adequate guidance for determining other NOR1 genes or that other NOR1 genes exist or have the same function as the NOR1 gene disclosed. Limiting the claims 5-9,14, and 15 to a transgenic mouse or mouse cell and deleting "a" preceding "NOR1" in claims 5,8,18 and 19 would overcome this rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1) Claims 5-8 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi (*Scientific American*, 1994, vol. 270, pp 34-41) in view of Maltais (February 2000, DNA and Cell Biology, Vol. 19, pages 121-130).

Capecchi taught transforming a cell with a nucleic acid construct comprising a disruption in the HoxA-3 gene, resulting in an inactivating insertion of a selective marker gene into the endogenous HoxA-3 locus, and using said cell to generate a mouse whose genome comprises a disruption in the HoxA-3 gene. Capecchi differs from the claimed invention in that the targeting construct does not disrupt the NOR-1 gene.

However, at the time the claimed invention was made, Maltais taught the nucleic acid sequence of the mouse TEC (NOR-1) gene (entire document and for further detail Figure 2 legend reference to GenBank Accession No. AF191211).

Accordingly, it would have been obvious for one of ordinary skill in the art at the time the claimed invention was made, to make cells and a knockout mouse having a disruption in a targeted gene as taught by Capecchi wherein the gene was TEC (NOR-1) as taught by Maltais. One of ordinary skill in the art would have been sufficiently motivated to replace the Hox3A gene with the TEC (NOR-1) gene, as it was an art-recognized goal to determine the physiological role of a gene of interest by the

generation of a knockout mouse. One of ordinary skill in the art would have been sufficiently motivated to disrupt the TEC (NOR-1) gene to determine its role in transcriptional regulation, as described by Maltais (entire document).

Note that absent any phenotypic requirements for the claimed transgenic mouse, the combination of the cited prior art is sufficient to make obvious the claimed invention. Capecchi discloses the applicability of gene targeting to many other genes so that a correlation can be drawn between the malfunctioning gene and the manifestation of disease (page 41, column 2, 2nd full paragraph).

Thus, the claimed invention is clearly *prima facie* obvious in the absence of evidence to the contrary.

2) Claims 5-10 and 14,15,18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Beach (*1999, USPN 5,919,997*) in view of Maltais (February 2000, DNA and Cell Biology, Vol. 19, pages 121-130).

Beach taught transforming a cell with a nucleic acid construct comprising a disruption in the INK4 gene, resulting in an inactivating insertion of a selective marker gene into the endogenous INK4 locus, and using said cell to generate a knockout mouse whose genome comprises a disruption in the INK4 gene (column 14, lines 61-66). Beach administered compounds to the transgenic knockout mice comprising a disruption in the INK4 gene to screen for agents that affect the INK4 mutant phenotype and modulate the expression or function of INK4 (column 26, lines 51-54 and claim 11). Beach differs from the claimed invention in that the targeting construct does not disrupt the NOR-1 gene.

However, at the time the claimed invention was made, Maltais taught the nucleic acid sequence of the mouse TEC (NOR-1) gene (entire document and for further detail Figure 2 legend reference to GenBank Accession No. AF191211).

Accordingly, it would have been obvious for one of ordinary skill in the art at the time the claimed invention was made, to make cells and a knockout mouse having a disruption in a targeted gene as taught by Beach wherein the gene was TEC (NOR-1) as taught by Maltais and to use said animals to screen for compounds that modulate NOR1 expression or function by assessing changes in the NOR1 mutant phenotype. One of ordinary skill in the art would have been sufficiently motivated to replace the INK4 gene with the TEC (NOR-1) gene, as it was an art-recognized goal to determine the physiological role of a gene of interest by the generation of a knockout mouse and to use the mouse to screen for agents that affects or ameliorates the mutant phenotype. One of ordinary skill in the art would have been sufficiently motivated to disrupt the TEC (NOR-1) gene to determine its role in transcriptional regulation, as described by Maltais (entire document) or to screen for modulators of NOR1 expression or function as taught by Beach.

Thus, the claimed invention is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is 703-305-5469. The examiner can normally be reached on 7:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on 703-305-4051. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234.

Valarie Bertoglio

Patent Examiner

DEBORAH J. REYNOLDS
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600